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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,326	SATO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed September 20, 2002 in Paper No. 9 is acknowledged and has been entered. Claims 1-8 have been amended.

2. The substitute specification filed September 20, 2002 as part of Paper No. 9 is acknowledged and has been entered.

3. The declaration under 37 CFR § 1.808(a) by Masao Haruna is acknowledged and has been entered.

4. Claims 1-8 are pending in the application and are currently under prosecution.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on September 20, 2002 is a duplicate of the previously filed IDS. The examiners have considered the references submitted with the IDS; however, although US Patent Application serial no. 09/269,232 has been considered, the application will not be included in the list of "References Cited" should a patent issue from this application because the application is not printed or publicly available.

Grounds of Obj ctions or Rej ctions Withdrawn

6. Unless specifically reiterated below, the grounds of objection or rejection set forth in the previous Office action mailed March 22, 2002 (Paper No. 7) have been withdrawn.

Claim Objections

7. Claim 6 is objected to because the marked-up copy thereof differs from the clean copy, as "method" is capitalized in the marked-up copy of the claim, but not in the clean copy.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for preventing at least one symptom of a hypercalcemic crisis, wherein said method comprises administering to a patient at least one substance capable of inhibiting the binding between PTHrP and a receptor thereof. However, the specification does not describe the production of a substance that is capable of preventing a symptom of a hypercalcemic crisis; furthermore, the specification does not describe the use of such a substance to prevent a symptom of a hypercalcemic crisis.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of

ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

Accordingly, because the claims encompass the use of a genus of variant species of substances capable of inhibiting binding of PTHrP to a receptor thereof, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, it appears the specification does not describe the use of a single member of the genus of substances capable of inhibiting the binding of PTHrP to a receptor thereof to prevent at least one symptom of a hypercalcemic crisis. Consequently, there is no factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings

or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

10. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for preventing or treating a patient having a hypercalcemic crisis, wherein said method comprises administering to said patient a substance that is capable of inhibiting the binding between PTHrP and a receptor thereof. However, the teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention to prevent or treat a symptom of hypercalcemia or an acute crisis thereof without having the need to perform additional, undue experimentation. Furthermore, the teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully making a substance that inhibits binding of PTHrP to a receptor thereof, which can be used effectively to prevent or treat a symptom of hypercalcemia or an acute crisis thereof without having the need to perform additional, undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claimed invention is not exemplified in the specification, not even prophetically. The specification discloses and exemplifies methods for making antibodies, including recombinant antibodies, that can be used to neutralize PTHrP, but the specification does not teach the use of such antibodies to prevent or treat hypercalcemia or an acute crisis thereof. As evidenced by the teachings of Rosen, et al (*Calcified Tissue International* **61**: 455-459, 1997), just because a substance is capable of binding PTHrP or a receptor thereof and neutralizing their activities by inhibiting binding of one to the other, it cannot be presumed the substance can be used effectively to prevent or treat hypercalcemia or an acute crisis thereof. In other words, the skilled artisan cannot predict whether a substance that is capable of inhibiting binding of PTHrP to a receptor thereof can be used effectively to prevent or treat hypercalcemia or an acute crisis thereof. Because of the lack of predictability associated with the art, as evidenced by the teachings of Rosen, et al, an amount of working exemplification, which is reasonably commensurate in scope with the claims, must be disclosed to meet the requirements set forth under 35 USC § 112, first paragraph. In the absence of any working exemplification and moreover, in the absence of any prophetic exemplification of the claimed invention that might serve to provide the guidance and direction necessary to enable the use of the invention in the absence of working exemplification, Applicant's disclosure cannot be regarded as sufficient.

In addition, the amount of guidance, direction, and exemplification is insufficient under 35 USC § 112, first paragraph, because one skilled in the art could not reasonably expect to successfully make a substantial number of the members of the genus of substances that are capable of inhibiting binding of PTHrP to a receptor thereof, which can be used effectively to treat, without having the need to perform additional, undue experimentation. The specification teaches methodology that can be used to make an antibody or a recombinant version thereof that inhibits binding of PTHrP to a receptor thereof, but the specification does not teach the methodology necessary to make any of the other substances that Applicants have contemplated for use in practicing the claimed invention. As a vast number of peptides and other small

molecules or low molecular weight substances might not be expected to inhibit binding of PTHrP to a receptor thereof, or to effectively prevent or treat hypercalcemia or an acute crisis thereof, sorting and identifying working and non-working embodiments of the claimed invention would require additional, undue experimentation, particularly since the specification does not exemplify the methodology by which one might do so.

Applicants' arguments have been carefully considered but not found persuasive for the reasons set forth above; but in particular, because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims, the skilled artisan could not have a reasonable expectation of success in practicing at least a substantial number of the embodiments of the claimed invention to prevent or treat a hypercalcemic crisis.

11. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 recite "[a] method for preventing or treating at least one symptom of hypercalcemic crisis". However, there does not appear to be proper and sufficient antecedent basis in the specification for recitation of this claim language. In addition, claims 1-8 recite "administering to a patient at least one substance", and claim 4 recites "wherein said substance is at least one of a fragment [...] or modified form of the fragment"; however, again, there does not appear to be proper and sufficient antecedent basis in the specification for recitation of this claim language. Therefore, recitation of such claim language appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

These issues might be resolved if Applicants were to point to specific disclosures in the specification that are believed to provide the necessary support for such claim language.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite for the reason set forth in the previous Office action. Applicants have traversed this ground of rejection, arguing that a "fragment" of an antibody is defined in the specification as "Fab, F(ab')2, Fv, or a single chain Fv (scFv) composed of a H-chain Fv fragment or a L-chain Fv fragment linked together through a suitable linker". Furthermore, Applicants have traversed this ground of rejection, arguing that a modified form of a fragment of an antibody is exemplified in the specification; however, this argument is not persuasive, since although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Moreover, the disclosed example of a modified form of a fragment of an antibody is merely exemplary, and does not serve to clearly and particularly delineate the metes and bounds of the invention.

Claim 4 is also indefinite because the claim recites the limitation "wherein the substance is at least one of a fragment of an anti-PTHrP antibody or a modified form of the fragment". The claim should properly read, "wherein the substance is at least one of a fragment of an anti-PTHrP antibody and a modified form of the fragment" (underlining added for emphasis).

In addition, claims 1-8 are indefinite because the former claims were drawn to a therapeutic agent comprising a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof, while the present claims are drawn to a method comprising administering to a patient a substance capable of inhibiting the binding of PTHrP to a receptor thereof. Presumably, the substance of the former claims would inhibit the binding of PTHrP to a receptor thereof once administered to a subject; however, as the substance of present claims is administered to a subject, and the substance is *only still capable* of inhibiting the binding of PTHrP to a receptor thereof, the metes and bounds of the invention cannot be ascertained, since it is unclear under what conditions the

claims require the administered substance to actually be able to inhibit binding of PTHrP to a receptor thereof.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 2, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosen, et al (*Calcified Tissue International* **61**: 455-459, 1997).

Rosen, et al teach a method that comprises administering to a patient a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof.

16. Claims 1, 2, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by WO-9200753-A1.

WO-9200753-A1 teaches a method that comprises administering to a patient a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof.

17. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,626,845-A.

US Patent No. 5,626,845-A ('845) teaches a method that comprises administering to a patient a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof. '845 teaches that a humanized antibody that binds specifically to PTHrP can be used to treat the symptomatic squalae of metastasis. '845 teaches an anti-PTHrP antibody is capable of neutralizing PTHrP, as evidenced by the showing that the antibody dramatically lowers the serum calcium levels of mice.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato, et al (*Journal of Bone and Mineral Research* **8**: 849-860, 1993) in view of US Patent No. 5,626,845-A for the reasons set forth in the previous Office action.

To the extent that Applicants' arguments are relevant to the traversal of the instant grounds of rejection, Applicants' arguments have been carefully considered, but not found persuasive. Applicants have argued that hypercalcemia differs from a "hypercalcemic crisis", or an acute hypercalcemic event; this argument is not found convincing. Besides, the claims state the intended use of the invention is to prevent or treat at least one symptom of hypercalcemic crisis; arguendo, if hypercalcemia can be differentiated from an acute crisis thereof, both conditions share at least one symptom that is expected to be ameliorated upon administering the substance to the patient.

Conclusion

20. No claims are allowed.

21. Applicants' amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
January 13, 2003

ANTHONY C. CAPUTA
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